

Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis

Problems compromise review's validity

EDITOR—Deeks et al say that celecoxib has improved gastrointestinal safety and tolerability compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs).¹ We have several concerns.

Firstly, Deeks et al reported the papers by Bensen et al, Zhao et al (1999), Simon et al, and Zhao et al (2000) as if they referred to four different trials.¹ The papers by Bensen et al and Zhao et al (1999) were, however, merely duplicate reports of one trial, whereas the papers by Simon et al and Zhao et al (2000) reported in duplicate on another trial. Deeks et al either included the same data more than once or mixed up unpublished data with unrelated publications.

Secondly, Deeks et al report similar relative risks for ulcer complications observed after six months in CLASS's two trials²: 0.54 (95% confidence interval 0.20 to 1.47) for study 035 (celecoxib *v* ibuprofen) and 0.56 (0.19 to 1.66) for study 102 (celecoxib *v* diclofenac), implying that it is appropriate to pool two trials by using comparator drugs of different cyclo-oxygenase-2 selectivity. According to the Food and Drug Administration (www.fda.gov), however, four events occurred in the celecoxib group and 11 in the ibuprofen group in study 035 (0.36, 0.12 to 1.14), whereas seven events occurred in the celecoxib group and nine in the diclofenac group in study 102 (0.78, 0.29 to 2.08).³ This implies that pooling these trials may be inappropriate.

Thirdly, Deeks et al's justification for considering only CLASS's six month results is problematic.⁴ Admittedly, data available from the FDA indicate that rates of patient withdrawal were different in the celecoxib and ibuprofen groups, implying that results for study 035 were unreliable at all time points. In accordance with Deeks et al, this trial should therefore have been excluded from all analyses. Contrary to Deeks et al, however, no relevant differences were found between celecoxib and diclofenac groups in study 102. The differences in duration of treatment between the celecoxib and diclofenac groups reported by Deeks et al merely relate to the fact that for half of the patients taking celecoxib (study 035) the maximum duration of treatment was 15 months, whereas for patients allocated to diclofenac in study 102 the maximum duration of treatment was only 12 months.⁴

Fourthly, patients with osteoarthritis or rheumatoid arthritis generally take NSAIDs for years. Therefore, Deeks et al's short term results are misleading. There is no evidence that in the long term celecoxib is more beneficial than diclofenac in avoiding severe gastrointestinal complications (relative risk for CLASS's complete follow up 1.10, 0.47 to 2.58).³

Peter Jüni senior research fellow in clinical epidemiology
juni@ispm.unibe.ch

Rebekka Sterchi research associate
Department of Rheumatology, University of Berne, 3010 Berne, Switzerland

Paul Dieppe professor of health services research
MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol BS8 2PR

Competing interests: None declared.

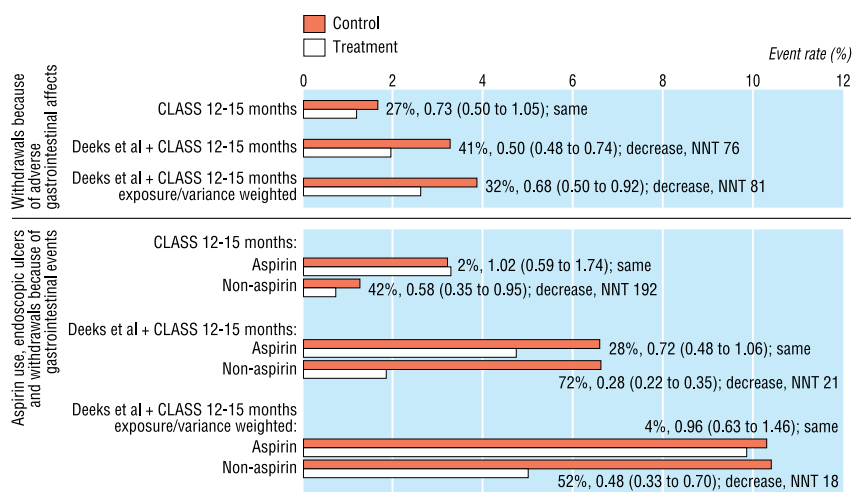
- Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002;325:619-23. (21 September.)
- Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA* 2000;284:1247-55.
- Jüni P, Rutjes AW, Dieppe P. Are selective COX 2 inhibitors superior to traditional NSAIDs? *BMJ* 2002;325:163-4. (20 July.)
- Jüni P, Rutjes AW, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.

Celecoxib's relative gastrointestinal safety is overstated

EDITOR—The meta-analysis by Deeks et al on celecoxib does not account for the 12-15 month data for the CLASS study compiled by the Food and Drug Administration.¹⁻⁴ Having abstracted these data and applied them to the Deeks analysis, we find that the picture changes markedly.

We also found the explanation for limiting the analysis of Deeks et al to CLASS's six month follow up to be unconvincing, insufficient to justify the post hoc changes in design, outcomes, and analysis.⁵ The FDA's analysis of CLASS was comprehensive, including accounting for the 12-15 month data. We also believe that the adverse gastrointestinal effects shown in figure 2 in the paper by Deeks et al should have included these 12-15 month CLASS data, which materially affect the results.

For withdrawals from both serious upper gastrointestinal events and endoscopic ulcers, the 12-15 month FDA data for CLASS showed no significant reduction in risk (relative risk 0.73, 95% confidence interval 0.50 to 1.05). Combining these data with the seven trials in figure 2 by Deeks et al and then adjusting for the much longer exposure time experienced in CLASS (12-15 months rather than weeks) decreases the overall reduction in relative risk to 32% (figure). These results indicate that, although celecoxib still causes significant reductions in gastrointestinal adverse events overall, reductions were appreciably less than suggested.



Celecoxib *v* non-steroidal anti-inflammatory drugs in randomised controlled trials. Values are relative risk reduction, relative risk (95% confidence interval). NNT=number needed to treat

Deeks et al reported no significant difference between use of low dose aspirin and no aspirin for endoscopic ulcers and for CLASS. But using the CLASS 12-15 month data implies that, whereas non-aspirin users had a significant 42% relative risk reduction, aspirin users showed no risk reduction (1.02, 0.59 to 1.74). The difference between the subgroups' relative risk reductions over the 12-15 months was significant ($P=0.03$).

Taken in their entirety (combining both endoscopic ulcers with CLASS's gastrointestinal withdrawals and ulcers), the significant differences between subgroups mentioned above persist. Including the 12-15 month CLASS data gave a non-significant 28% relative risk reduction for aspirin use, compared with 72% for non-aspirin use—a significant difference between reductions in relative risk. Adjusting for CLASS's longer exposure gave again a non-significant 4% relative risk reduction for aspirin users (exposure/variance weighted relative risk 0.96, 0.63 to 1.46) *v* 52% for non-aspirin use ($P < 0.01$) (figure).

We disagree that celecoxib's benefits extend equally to aspirin users. Pending any further information, we concur with the current precautionary recommendation of the National Institute for Clinical Excellence, to withhold celecoxib from aspirin users. Our analysis can be found on PHARMAC's website (www.pharmac.govt.nz). We believe that the data by Deeks et al, which indicate favourable gastrointestinal safety for celecoxib, need careful scrutiny.

Scott Metcalfe *public health physician*

Sean Dougherty *analyst*

Wayne McNee *chief executive*

Pharmaceutical Management Agency (PHARMAC), Level 1 Old Bank Chambers, 98 Customhouse Quay, PO Box 10 254, Wellington 6001, New Zealand

Competing interests: None declared.

PHARMAC is the New Zealand government agency responsible for funding community pharmaceuticals.

- Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002;325:619-23. (21 September.)
- Jones R. Efficacy and safety of COX 2 inhibitors. *BMJ* 2002;325:607-8. (21 September.)
- Witter J. Celebrex capsules (celecoxib). Medical officer review. US Department of Health and Human Services Food and Drug Administration, 2000. www.fda.gov/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 1 Jun 2002).
- Lu HL. Celebrex capsules (celecoxib). Statistical reviewer briefing document for the advisory committee. US Department of Health and Human Services Food and Drug Administration, 2000. www.fda.gov/dockets/ac/01/briefing/3677b1_04_stats.doc (accessed 1 Jun 2002).
- Juni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.

Authors' reply

EDITOR—The CLASS study has caused furore because of the absence of longer term follow up in the original publication and subsequent revelations that the benefits of celecoxib seem to diminish with longer follow up.^{1,2} Both Juni et al and Metcalfe et al therefore question our focus on the six month follow up data.³ This trial was

Withdrawals in CLASS study based on report by medical officer of Food and Drug Administration⁴

Reasons for withdrawal	No (%) of patients taking celecoxib (n=3987)	No (%) of patients taking diclofenac (n=1996)	% difference from celecoxib (95% CI, P value)	No (%) of patients taking ibuprofen (n=1985)	% difference from celecoxib (95% CI, P value)
6 month follow up*					
Total withdrawn	1611 (40.4)	848 (42.5)	2.1 (−0.6 to 4.7, $P=0.12$)	936 (47.2)	6.7 (4.1 to 9.4, $P<0.0001$)
Adverse events	732 (18.4)	443 (22.2)	3.8 (1.7 to 6.0, $P=0.0004$)	379 (19.1)	0.7 (−1.3 to 2.8, $P=0.49$)
Treatment failure or non-compliance†	854 (21.4)	395 (19.8)	−1.6 (−3.8 to 0.5, $P=0.14$)	546 (27.5)	6.1 (3.7 to 8.4, $P<0.0001$)
Full follow up*					
Total withdrawn	2208 (55.4)	1057 (53.0)	−2.4 (−5.1 to 0.3, $P=0.08$)	1294 (65.2)	9.8 (2.0 to 6.7, $P=0.0002$)
Adverse events	905 (22.7)	540 (27.1)	4.4 (2.0 to 6.7, $P=0.0002$)	461 (23.2)	0.5 (−1.7 to 2.8, $P=0.65$)
Treatment failure or non-compliance†	1276 (32.0)	506 (25.4)	−6.6 (−9.0 to −4.3, $P<0.0001$)	821 (41.4)	9.4 (6.8 to 12.0, $P<0.0001$)

*Does not account for differential follow up of two component trials but is best analysis possible from data available.

†Non-compliance included intermittent use of proton-pump inhibitor or H₂ receptor antagonists, use of additional NSAIDs, or taking less than 70% of prescribed drugs.

included for only two of the 17 outcomes assessed in our review.

The time point for analysis was pre-specified based on consideration of the CLASS protocol. This decision was made before the trial analysis was completed; we were therefore not influenced by the study findings. With hindsight we agree that celecoxib seems most effective at six months, although even here the significance is borderline.³

The six month data provide the most robust findings from this study. Although it is important for the results at full follow up to be available, one must consider the biases to which they are susceptible. Four issues complicate interpretation beyond six months:

- It was never intended to follow all participants for 12 months: follow up was planned to terminate once the target number of events had occurred and at least six months after the last participant had been recruited.⁴ This was our rationale for preselecting six months.³ Owing to unexpectedly low event rates, follow up was extended by three months in half the study, but many participants still had less than 12 months of follow up when the study was terminated. Any analysis beyond six months thus requires the use of time to event methods using raw data: presentation of crude rates, as by Juni et al and Metcalfe et al, is misleading.

- Withdrawal rates differed significantly between ibuprofen and celecoxib throughout follow up, and, contrary to Juni et al's assertion, reasons for withdrawal differed significantly between diclofenac and celecoxib.⁴ As shown in the table, the magnitude of these differences increased as follow up progressed, indicating that earlier results were more robust. More participants withdrew because of adverse effects with diclofenac: if they had a higher risk of gastrointestinal adverse the results will be biased. It is impossible to ascertain whether this is the case: the tests of informative censoring undertaken by the Food and Drug Administration's statistician do not directly address this question.⁵

- The trial did not follow the intention to treat principle of collecting outcome data on participants withdrawn from treatment: events were included only if they occurred within 48 hours of terminating study treatment.^{4,5} As withdrawals accrued differentially with increasing follow up, the numbers at risk decreased differentially between the groups. Analysis of crude event rates again ignores this and is biased.

- As mentioned by Juni et al, the study contained two trials, one randomising between celecoxib and diclofenac, the other between celecoxib and ibuprofen. Correct analysis requires that participants are directly compared only with those with whom they were randomised. No stratified analyses are presented in the study report, neither are the required data readily extractable. Juni et al succeeded in extracting stratified data from the detailed descriptions of the event in the report of the Food and Drug Administration for the main outcome. For our six month analysis, stratification makes no difference to the overall estimate, but it will be more important for the analysis at final follow up because of the differing duration of the two component trials.

Metcalfe et al choose to meta-analyse diverse outcomes from the trials. They pooled the CLASS symptomatic ulcers, bleeding, obstructions, and perforations (safety outcomes) with treatment withdrawals due to adverse events (tolerability outcomes), and then with non-symptomatic ulcers (a surrogate marker of safety). They also differentially weight study results by using non-standard methods. Although this has narrowed confidence intervals, it is difficult to know what the results for these composite outcomes mean. Additionally, based on comparing the confidence intervals that they quote, the first difference between aspirin and non-aspirin that they claim as significant (relative risk 1.02, 95% confidence interval 0.59 to 1.74 *v* 0.58, 0.35 to 0.95) is not ($P=0.13$). The second P value they quote is also wrong ($P=0.02$).

We can confirm that the errors Juni et al point out are not duplicate publications but

simple labelling errors that do not affect the results. A correction is available on bmj.com.⁶

We believe that we have reported the best data currently available in our review of celecoxib. As we previously indicated, despite the large numbers randomised in CLASS, little is known with much certainty about the effectiveness of celecoxib at and beyond six months' follow up. Although the estimates of protection up to and at six months favour celecoxib, the confidence intervals are wide, and withdrawal rates are high. Proper analysis and presentation of full results from CLASS will resolve some of the difficulties discussed above, but further long term larger trials are inevitably required.

Jonathan J Deeks senior medical statistician
Jon.Deeks@cancer.org.uk

Lesley A Smith research fellow
Lesley.Smith@cancer.org.uk

Centre for Statistics in Medicine, Institute of Health Sciences, Oxford OX7 3LF

Matthew D Bradley associate director
Pfizer Global Research and Development,
Sandwich, Kent CT13 9NJ

Competing interests: LAS is employed on a fellowship funded by Pfizer. JJD has acted as a paid consultant to Pfizer and Pharmacia. MDB is an employee of Pfizer.

- 1 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *Celecoxib long-term arthritis safety study*. *JAMA* 2000;284:1247-55.
- 2 Juni P, Rutjes AW, Dieppe P. Are selective COX 2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.
- 3 Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002;325:619-23.
- 4 Witter J. *Celebrex capsules (celecoxib)*. Medical officer review. US Department of Health and Human Services Food and Drug Administration, 2000. www.fda.gov/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 1 Jun 2002).
- 5 Lu HL. *Celebrex capsules (celecoxib)*. Statistical reviewer briefing document for the advisory committee. US Department of Health and Human Services Food and Drug Administration, 2000. www.fda.gov/dockets/ac/01/briefing/3677b1_04_stats.doc (accessed 1 Jun 2002).
- 6 Deeks JJ. Study reports: clarification, corrections, and additional sources. Electronic response to: Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis. *bmj.com* 2002. bmj.com/cgi/eletters/325/7365/619#26882 (accessed 30 Dec 2002).

General practitioner screening for excessive alcohol use

Paper enables open debate about a complex intervention

EDITOR—The response on bmj.com to the paper by Beich et al is probably the first time that open debate has taken place about how alcohol screening and brief intervention for excessive drinkers fits into everyday practice. The strength of feeling is unmistakable, from a general practitioner's scepticism about intervention itself to a seemingly flat refusal from a group of leading European alcohol researchers to accept the validity of a qualitative study that reported concerns expressed by practitioners.¹⁻³ Views are differing about how far public health initiatives can and should be integrated into everyday practice.

Beich sent me his group's paper for comment, and my impression was of a diligent researcher who sat in the uncomfortable zone between research and everyday practice. His findings struck a chord with me, as I had encountered many of the same issues when running an outcome study in the mid-1980s. Hence my attempts on several occasions to suggest modifications to preventive work on alcohol consumption.⁴ Beich et al's paper seemed to more than match other qualitative studies for methodological adequacy. To dismiss the findings as largely a byproduct of poor research methods seems curiously overstated.²

General practitioners are being cajoled to change their consulting behaviour on many fronts. At the centre of this is their relationship with their patients. In antibiotic prescribing, for example, public health experts have found it difficult to achieve changes in prescribing without taking on board the challenges inside the consultation.⁵ Similar lessons probably apply in alcohol consumption. Just as it is for patients, changing behaviour is a tricky business. Listening to general practitioners is an important first step, and there is probably no simple, technical solution to brief intervention (it is a far from simple intervention).

With the benefit of hindsight, it is regrettable that so many controlled trials have been published on screening and brief alcohol intervention without prior attention to the concerns of general practitioners, which is precisely the issue that both Beich et al and researchers of the World Health Organization are now struggling with.² If their conclusions about screening and intervention differ, then the priorities for future research are now clearly marked out. General practice interventions should be designed with the views of general practitioners firmly in mind, and the call from the consulting room of Millares in this correspondence² might be a good starting point.

Stephen Rollnick senior lecturer
Communication Skills Unit, Department of
General Practice, University of Wales, College of
Medicine, Cardiff CF23 9PN
rollnick@cf.ac.uk

- 1 Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview and study of the experiences of general practitioners. *BMJ* 2002;325:870-4. (19 October).
- 2 Millares P. Lifestyle advice. Electronic response to Screening and brief intervention for excessive alcohol use. *bmj.com* 2002. bmj.com/cgi/eletters/325/7369/870#26363 (accessed 9 Dec 2002).
- 3 Seppä K, Anderson P, Gual A, Heather N, Kaner E. Implementation of brief alcohol intervention depends on thorough preparation and proper training. Electronic response to Screening and brief intervention for excessive alcohol use. *bmj.com* 2002. bmj.com/cgi/eletters/325/7369/870#26876 (accessed 9 Dec 2002).
- 4 Rollnick S, Butler C, Hodgson R. Brief alcohol intervention in medical settings: concerns from the consulting room. *Addict Res* 1997;5:331-42.
- 5 Butler C, Rollnick S, Kinnerley P, Jones A, Stott N. Reducing antibiotics for respiratory tract symptoms in primary care: consolidating "why" and considering "how." *Br J Gen Pract* 1998;48:1865-70.

General practitioners' experiences are important

EDITOR—Beich et al report on a largely overlooked but crucial, component of the population based prevention of alcohol related

harm.¹⁻² The experience of general practitioners in screening and delivering brief interventions was problematic. Beich et al call into question the model of universal screening as a precursor to brief intervention. But alternative explanations must at least be considered for the evident discomfort in establishing rapport with patients. Furthermore, forming a judgment on the adequacy of training provided from this report is difficult.

Cartwright et al found that low therapeutic commitment by general practitioners in relation to alcohol interventions derived from anxieties including legitimacy of their role (seeing it as part of the role) and adequacy of it (having requisite knowledge and skills).³ These general practitioners' views on young people indicate problems with role legitimacy. Articulated difficulties in delivering interventions may entail both role adequacy and support issues.³ The claimed effect on the relationship between doctor and patient is more suggestive of a lack of confidence on the part of the doctor.

Maybe general practitioners require additional skills to initiate conversations about drinking after applying the screening instrument. This is a testable hypothesis. Conversations about drinking may take place in many ways in general practice, and the universal screening model might be a mechanical way of approaching the subject. Sensitively raising the subject, either by facilitating for patients to initiate talks or by practitioners doing so, may be a key characteristic of good clinical practice, but it will be challenging to study.

The resounding vote of no confidence in continuation of this alcohol work, both in the trial and in routine practice, is startling. It is also worrying and should prompt a serious strategic rethink. Even this volunteer sample of general practitioners found the work fraught with difficulty, and we urgently need to know how generalisable these data are. Practitioners' experience of, and views on, alcohol screening and brief intervention now need urgent further exploration, and interventions targeting the motivation of general practitioners themselves may be necessary. Context bound training,⁴ in which the actual experience of clinical practice forms the basis of the curriculum, may represent another promising way forward.

Jim McCambridge health services research
co-ordinator
j.mccambridge@iop.kcl.ac.uk

Francis Keaney clinical research worker
John Strang director
National Addiction Centre, Institute of Psychiatry,
Maudsley Hospital, London SE5 8AF

Stephen Rollnick senior lecturer
Department of General Practice, University of
Wales, College of Medicine, Cardiff CF23 9PN

- 1 Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. *BMJ* 2002;325:870-4. (19 October).
- 2 Edwards G, Anderson P, Babor TF, Casswell S, Ferrence R, Giesbrecht N, et al. *Alcohol policy and the public good*. Oxford: Oxford Medical Publications, 1994.
- 3 Cartwright AJK. The attitudes of helping agents towards the alcoholic client: the influence of experience, support, training and self-esteem. *Br J Addict* 1980;75:413-31.
- 4 Rollnick S, Kinnerley P, Butler C. Context-bound communication skills training: development of a new method. *Med Educ* 2002;36:377-83.

Brief screening tools should be used in general practice

EDITOR—Although Beich et al say that general practitioners may experience problems in implementing screening and brief intervention into their regular practice, it is encouraging that they saw counselling patients about their consumption as important.¹ In this case, although screening was effective (with almost 16% of patients identified as hazardous drinkers), the general practitioners were uncomfortable with implementing the intervention.

AUDIT is often regarded as the gold standard for alcohol screening, but the time it takes to administer and score may render it unsuitable for use in a busy setting.² Brief intervention is effective at reducing alcohol consumption,³ but again, the time it takes to implement can be prohibitive in short consultations.

In our work at St Mary's Hospital we have found that brief screening instruments such as the Paddington alcohol test (PAT) are appropriate for identifying patients who may benefit from further advice.⁴ The test takes less than one minute to administer and has good sensitivity and specificity compared with AUDIT.⁵ In a recent clinical trial we found that 64% of hazardous drinkers were willing to accept advice about their alcohol consumption. Simply highlighting the effect of a patient's current consumption on future health may act as the briefest of brief interventions.

The clinicians who undertake this screening as part of routine practice offer all hazardous drinkers an appointment with our resident alcohol health worker. Previous research has found that up to 50% of patients will attend such an appointment, with up to 65% of them reducing their alcohol consumption. Patients who do not accept the appointment are given a copy of "Think about drink" and a card with the telephone numbers of local alcohol agencies.

Brief screening tools should be used in general practice, perhaps as part of a patient's initial registration, or when patients present to the practice with conditions that are associated with excessive consumption.⁵ Patients identified as hazardous drinkers can then be offered an intervention either by an external alcohol health worker or other appropriate (local) practitioner.

Robert Patton *REDUCE project co-ordinator*
Department of Psychological Medicine, Faculty of Medicine, Imperial College of Science, Technology and Medicine, London W2 1PD

Robin Touquet *consultant in accident and emergency medicine*
St Mary's Hospital, London W2 1NY

- 1 Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. *BMJ* 2002;325:870-4. (19 October.)
- 2 D'Onofrio G, Bernstein E, Bernstein J, Woolard RH, Brewer PA, Craig SA, et al. Patients with alcohol problems in the emergency department, part 2: intervention and referral. *Acad Emerg Med* 1998;5:1210-7.
- 3 Wilk AJ, Jensen NM, Havighurst. Meta-analysis of randomised control trials addressing brief interventions in heavy drinkers. *J Gen Intern Med* 1997;12:274-83.
- 4 Huntley JS, Blain C, Hood S, Touquet R. Improving detection of alcohol misuse in patients presenting to an accident and emergency department. *Emerg Med J* 2001;18:99-104.

5 Hodgson R, John B, Alwyn T, Newcombe RG, Waller S, Thom B, et al. Fast screening for alcohol misuse. *Alcohol Insight* 1998;5. (Alcohol Education and Research Council project report.)

Antiretroviral therapy: new solutions bring new problems

EDITOR—Jordan et al's meta-analysis of anti-retroviral drug regimens supports the continued use of triple therapy for established HIV infections in adolescent and adult patients.¹ While any advance in combating the progression of HIV is clearly welcome, the potential side effects of treatment need to be known.

Antiretroviral inhibitor use is associated with a range of morphological and metabolic alterations. Altered glucose homeostasis may result in the development of frank diabetes mellitus in up to 7% of patients. Lipid metabolism is also affected and may lead to changes in serum lipid concentrations, which may contribute to an increase in the occurrence of pancreatitis.²

Lipodystrophy is a commonly encountered problem associated with antiretroviral therapy and has been found in 50-60% of patients after as little as one year of drug treatment. Characteristic morphological changes include central, intra-abdominal fat deposition, as well as fat deposition in the dorso-cervical ("buffalo hump") and supra-clavicular areas. Atrophy of peripheral fat, including on the face, can occur separately or in combination with central fat deposition (figure). Cessation of treatment does not seem to reverse these effects.

Lipodystrophy is not life threatening, but it is often severely psychologically distressing to patients. Increasingly they seek surgical intervention in the absence of other effective treatments, which has provided a new and difficult challenge to reconstructive surgeons. No consensus currently exists on how best to manage these problems, but plastic surgery may correct some symptoms in some cases. Suggested treatments include facial implants (dermis-fat graft, autologous fat, prosthetic materials) and suction-assisted lipectomy for superficial fat deposits (figure).^{3,4} Initial improvements in appearance are promising, but data on long term outcome are not yet available.

Conservative methods of managing lipodystrophy are currently limited. A cautious approach to surgical procedures in this group is warranted as complications such as



Facial lipodystrophy before (left) and after (right) treatment

soft tissue infection may have serious implications in this vulnerable, potentially immunocompromised group, possibly requiring the cessation of anti-retroviral therapy.

Joanne L Atkins *registrars plastic surgery*
Royal Free Hospital, London NW3 2QG
joannepalazzo@aol.com

Simon Eccles *clinical fellow cranial facial surgery*
Chelsea and Westminster Hospital, London SW10 9NH

Peter E M Butler *consultant plastic surgeon*
Royal Free Hospital

- 1 Jordan R, Gold L, Cummins C, Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in anti-retroviral combination therapy. *BMJ* 2002;324:757-60. (30 March.)
- 2 Wanke CA, Falutz JM, Shevitz A, Phair JP, Kotler DP. Clinical evaluation and management of metabolic and morphological abnormalities associated with human immunodeficiency virus. *Clin Infect Dis* 2002;34:248-59.
- 3 Wechselberger G, Sarletti M. Dermis-fat graft for facial lipodystrophy in HIV-positive patients: Is it worthwhile? *Ann Plast Surg* 2001;47:99-100.
- 4 Wolford FG, Cetrulo CL, Nevarre DR. Suction-assisted lipectomy for lipodystrophy syndromes attributed to HIV-protease inhibitor use. *Plast Reconstr Surg* 1999;104:1814-22.

Model for Bangalore helped disseminate information to doctors in India

EDITOR—In their editorial last year Langer and Villar described the promotion of evidence based practice in maternal care.¹ Recon Healthcare's model for Bangalore was developed to disseminate knowledge from the World Health Organization's reproductive healthcare library to doctors caring for women's health in India.

The information is stored in electronic form and updated annually and is available free of cost to developing countries (www.update-software.com/rhl/). Methods needed to be developed to disseminate the information to doctors in India. In developing countries interaction between academia and industry has therefore become an effective way of spreading knowledge rapidly to doctors.

At Recon Healthcare the medical department worked jointly with marketing executives and established a good rapport with doctors specialising in women's health care. Printouts of three relevant topics were given to doctors, who marked their choice and sent the form to the medical department through the marketing executive. In this way, knowledge from the WHO library resource was communicated to 1346 doctors across India in only seven months. When we asked 1076 doctors for feedback, 61 responded, most of them (89%) finding the information useful. We did not send any reminder.

In our department, hardware and software as well as internet access are used for routine activities and were used for Recon Healthcare's Bangalore model, without incurring extra expenditure in establishing the dissemination facility. The only expenses incurred were charges for postage, stationery (including printer cartridges), and paper. The cost of disseminating medical information works out at roughly 60p per doctor. So this model is cost effective.

With the method established in Recon Healthcare's Bangalore model, it should be possible for academia and industry to interact to spread medical knowledge to many doctors in India in the shortest possible time. Our model has shown that this is possible and workable.

C B Sridhar *senior medical adviser*
drsridhar@zydusrecon.com

Deena Suresh *manager, medical services*
Recon Healthcare, 2/2, South Cross Road,
Basavanagudi, Bangalore 560004, India

1 Langer A, Villar J. Promoting evidence based practice in maternal care. *BMJ* 2002;324:928-0.

Depressed patients need more than drugs and psychiatrists

EDITOR—Rost et al conducted a randomised controlled trial of ongoing treatment of depression in primary care, and Stroebele in response argued that it would make more sense for a patient to see a psychiatrist once and receive drug treatment if necessary for three or six months.^{1 2}

I do not believe a psychiatrist can make an accurate diagnosis after a single visit. Patients do not start to reveal themselves until a genuine trust and rapport have been established. Information gathered on an initial visit is likely to be extremely superficial and inadequate simply because the patients are depressed. They are not thinking clearly and usually forget to tell their doctors the most important things the doctors need to know.

I have seen too many misdiagnoses and bad prescribing of drug treatments. The pharmaceutical monographs available on drugs are often based on human trials in healthy male participants who are taking no other drugs. Therefore when a new drug enters the market, all its possible interactions, adverse effects, and contraindications have not yet surfaced. Doctors are poor at reporting adverse effects, so they are often never published. Unexpected paradoxical reactions can kill people or make them wish they were dead. This has happened to people I know who were being treated for depression.

It can be difficult to find the correct drug and dosage the first time. People taking any kind of drug, particularly psychoactive drugs, need to be monitored closely and questioned carefully and regularly until the effectiveness of the drug is determined and any adverse side effects have been evaluated.

Finally, many people cannot call on active networks for support, and family doctors have neither the time nor the training to help a person cope with depression.

Sharon J Williams *retired psychiatric nurse*
912-1333 Bloor Street East, Mississauga, ON,
Canada L4Y 3T6
envisage@sympatico.ca

- 1 Rost K, Nutting P, Smith JL, Elliott CE, Dickinson M. Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. *BMJ* 2002;325:934-9. (26 October.)
- 2 Stroebele RB. Depression: a disease requiring a psychiatrist and drugs? Electronic response. *bmj.com* 2002. www.bmj.com/cgi/eletters/325/7370/934#26540 (accessed 28 Jan 2003).

Host should also protect students on electives from HIV

EDITOR—Tilzey and Banatvala revisit the question of protecting medical students from HIV infection during their elective studies.¹ They found that most medical schools in the United Kingdom had updated their policies to minimise the risk to which their students were exposed while on elective. Medical schools now advise students to take HIV post-exposure starter packs, to restrict attachments to areas with a high prevalence of HIV, and not to undertake risky procedures in patients from such areas.

We agree that medical schools have a duty to ensure that their students are appropriately advised as well as treated should inoculation occur. But it is equally imperative for all institutions that take elective students to develop effective and practical policies that minimise risk while maximising experience, particularly when students are required to pay fees during their attachments.

South Africa is a popular choice for elective students despite the high prevalence of HIV.² Measures have been put in place to reduce the risk and possible sequelae of accidental inoculation. All foreign students spending their elective attachment in this trauma unit are required to undergo induction in preventing and managing needlestick injuries. No student may participate in any trauma resuscitation or open surgical procedure without full universal barrier precautions. Specific protocols have been laid down about the handling of sharps. Weekly video audit of trauma resuscitation is used to identify violations of the protocol and rectify omission.³ Immediate post-exposure prophylaxis is available 24 hours a day, as is counselling from a dedicated HIV specialist nurse.

These measures are especially pertinent because of the high prevalence of HIV in our local population, but they should be regarded as a minimum for any institution hosting elective medical students, whether in Johannesburg, South Africa, or Liverpool, United Kingdom.

Nigel R M Tai *trauma fellow*
nigeltai@mweb.co.za

Sue Nielson *trauma coordinator*
Trauma Unit, Johannesburg General Hospital,
Johannesburg, South Africa

Ken Boffard *professor*
Department of Surgery, University of the
Witwatersrand, Private Bag X39, Johannesburg
2000, South Africa

- 1 Tilzey AJ, Banatvala JE. Protection from HIV on electives: questionnaire survey of UK medical schools. *BMJ* 2002;325:1010-1. (2 November.)
- 2 Bowley DM, Cherry R, Snyman T, Vellema J, Rein P, Moeng S, et al. Seroprevalence of the human immunodeficiency virus in major trauma patients in Johannesburg. *S Afr Med J* 2002;92:792-3.
- 3 Brooks AJ, Phipson M, Potgeiter A, Koertzen H, Boffard KD. Education of the trauma team: video evaluation of the compliance with universal barrier precautions in resuscitation. *Eur J Surg* 1999;165:1125-8.

Disposal of remains of fetuses of under 24 weeks' gestation

EDITOR—I write as the medical referee to the Wakefield cremation authority about the disposal by cremation of the remains of fetuses of less than 24 weeks' gestation.

Although I understand the emotive reasons for hospital authorities wishing to find a more sensitive way of disposing of fetuses of less than 24 weeks' gestation, it is important to recognise that currently such disposals are outside the scope of the law as it relates to cremation. I therefore find it difficult to understand how a cremation authority can legally undertake cremation of fetuses, which are, and will remain until the law is changed, clinical waste, however distasteful this fact is.

Hospital authorities are currently seeking an extension to this practice to include the disposal by cremation of social terminations (abortions) and the contents of fetal sacs, which are also by definition clinical waste. The situation is even more confusing when the policy document of the Institute of Burial and Cremation Authorities that relates to fetal remains contradicts current legislation on cremation and specifically recommends that the medical referee should sign a form F, which is a statutory document.

I am concerned and surprised that cremation authorities and the Institute of Burial and Cremation Authorities, in attempting to respond to these emotive issues are placing themselves and medical referees in an invidious position. Other than for quasi-legal reasons there seems to be no requirement for the involvement of a medical referee or the production of a statutory form F in these cases.

Should cremation authorities and the Institute of Burial and Cremation Authorities still deem it appropriate to obtain a medical referee's signature, then an appropriate form, which is not a statutory document, could be designed for this purpose. It is apparent that a variety of working practices currently exist, which differ between cremation authorities—a situation that is totally unsatisfactory. Urgent consideration should be given to redressing these irregular practices to ensure that the reputation and integrity of cremation authorities and medical referees is not compromised.

R G Forster *medical referee for Wakefield Cremation Authority*
Wakefield Metropolitan District Council,
Cemeteries and Crematoria Department, Civic
Centre, Castleford, West Yorkshire WF10 4JH

bmj.com

Letters appearing here are an edited selection of rapid responses originally posted on *bmj.com*

We ask for all letters to the editor to be submitted as rapid responses via *bmj.com*. For advice see: *bmj.com/rapidresponses*